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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 09/641,081 | 08/16/2000 | Carsten Rosenow | 3334.2 | 3725 |

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AFFYMETRIX, INC
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| EXAMINER | |
|---|---|
| ZHOU, SHUBO | |
| **ART UNIT** | **PAPER NUMBER** |
| 1631 | |

DATE MAILED: 06/07/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/641,081 | ROSENOW ET AL. | |
| | Examiner | Art Unit | |
| | Shubo (Joe) Zhou | 1631 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *17 December 2004 and 10 March 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-9* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-9* is/are rejected.

7)☒ Claim(s) *3* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *15 January 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

## DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 12/17/04 has been entered. The amendments filed 3/10/05 is also acknowledged and entered.

2. The rejection of claims 6-9 under 35 USC 112, second paragraph as being indefinite in the previous Office action mailed 6/15/04 is hereby withdrawn in view of applicants amendment to claim 6.

3. The rejection of claims 1-9 under 35 USC 103(a) in the previous Office action mailed 6/15/04 is hereby withdrawn in view of applicants' statement that the Lockhart et al. reference (US 6040138) is not prior art because, at the time the invention was made, the subject matter of the Lockhart reference and the present invention were owned by, or subject to an obligation of assignment to, Affymetrix, Inc. See page 4 of the communication filed 12/17/04.

4. It is noted that a proposed claim amendment was filed on 12/9/04 apparently intended to be unofficial for discussion purpose only. Although no formal interview discussing the proposed

claim amendments has been made, the amendment is still considered as unofficial and the instant Office action is based on the claim listing filed 3/10/05.

***Claim Rejections-35 USC § 112***

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 1-9 are rejected under 35 U.S.C. 112 , second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The meaning of the phrase ""above a threshold value" in claim 1 and its dependent claims is unclear. It is not clear whether the threshold value is a value in terms of the number of probes hybridizing as compared to non-hybridized probes, or a value in terms of hybridizing intensity.

Claim 3 is dependent from itself. The metes and bounds of the claim, as currently written, is unclear because the phrase 'said oligonucleotides" recited in the claim lacks antecedent basis.

The meaning of the phrase "wherein hybridization of said probes targeting said sub-region is similar" in claim 6 and its dependent claims 7-9 is unclear. It is not clear what is similar: the hybridization signal intensities of the probes or the pattern of the hybridization, or else. Further, The term "similar" is a relative term that renders the claim indefinite. The term is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

7. Clarification of the metes and bounds of the phrases are required.

***Claim Rejections-35 USC § 103***

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

9. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

10. Claims 1-7 and 9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Leary et al. (WO 99/67422, 29 December 1999) in view of Lockhart et al. (WO 97/10365, 20 March 1997).

The claims are drawn to a method of identifying a transcribed region in a genome comprising hybridizing probes to transcripts from a genome and identifying a transcribed region if the hybridization signal between a probe and a transcript is above a threshold value.

Leary et al. disclose a method for mapping the position of individual transcripts from a genome comprising hybridizing a plurality of nucleic acid probes with a nucleic acid sample

wherein the sample comprises transcripts from the genome and the probes are from an area of the genome (page 4, first paragraph) and such probes are immobilized to a substrate (pages 7-8, the bridging paragraph). Leary et al. also disclose that the probes for hybridization are overlapping probes from a genomic region. See page 5. Leary et al. do not explicitly recite a threshold value for the hybridization signal of a region, above which, the region would be considered as transcribed.

Lockhart et al. teach a method of monitoring gene expression by hybridization of transcripts to high density oligonucleotide arrays. The method comprises hybridizing test transcripts to genomic probes immobilized onto substrates (page 3, Summary of the invention). To reduce the signal/noise ratio, Lockhart et al. teach using different control probes including normalization controls, expression level controls and mismatch control (pages 6-7 and 34-35).

Lockhart et al. state (page 39):

> The oligonucleotide array is hybridized to a sample containing target nucleic acids having subsequences complementary to the oligonucleotide probes and the difference in hybridization intensity between each probe and its mismatch control is determined. Only those probes where the difference between the probe and its mismatch control exceeds a threshold hybridization intensity (e.g. preferably greater than 10% of the background signal intensity, more preferably greater than 20% of the background signal intensity and most preferably greater than 50% of the background signal intensity are selected.

A person having ordinary skill in the art at the time the invention was made would therefore have been motivated by Lockhart et al. to modify Leary et al. to include all the control probes including the mismatch probes and to use a threshold with each control probe as suggested by Lockhart et al. in order reduce the signal/noise ratio.

As to claims 2 and 3, Leary et al. disclose that the probes of the genomic fragments can be oligonucleotides of 20 or more bases long to be immobilized onto a substrate (page 9, last paragraph, and the bridging paragraph of pages 7-8).

As to claims 4-5, Lockhart et al. disclose that the mismatch probes used as control probes comprise one or more mismatch at the center of the oligonucleotides, and provide control for non-specific binding. See pages 36.

Claim 6 recites "identifying a sub-region wherein hybridization of said probes targeting said sub-region is similar, thereby indicating said sub-region as said transcribed region. Leary et al. describe in Figure 1 graphically the method of mapping a transcript to a genome. Linear and overlapping fragments were fixed onto a substrate as dots wherein the genomic location for each dot is known. Transcripts from a sample are hybridized to the probes and similar patterns of hybridization, i.e. "bold" signals on the substrate, are considered as positive hybridization, indicating that the particular sub-regions represented by these genomic probes are transcribed.

As to claims 7 and 9, which recite bacteria and prokaryotes, Leary et al. disclose that the preferred embodiments in their method include using genomic fragments of bacterial species, most particularly a human pathogen such as Streptococcus, a prokaryote. See page 10, last paragraph.

11. Claim 8 is rejected under 35 U.S.C. 103(a) as being unpatentable over Leary et al. (WO 99/67422, 29 December 1999) in view of Lockhart et al. (WO 97/10365, 20 March 1997), as applied to claims 1-7 and 9 above, and further in view of Darnell et al. (Molecular Cell Biology, Scientific American Books, 1986).

Claim 8 is drawn to a method of identifying a transcribed region in a genome comprising hybridizing probes to transcripts from a genome and identifying a transcribed region if the

hybridization signal between a probe and a transcript is above a threshold value. The claim recites that the transcribed region is an operon.

As applied to claims 1-7 and 9 above, the combination of Leary et al. and Lockhart et al. discloses a method of identifying a transcribed region in a genome comprising hybridizing probes to transcripts from a genome and identifying a transcribed region if the hybridization signal between a probe and a transcript is above a threshold value.

Leary et al. and Lockhart et al. do not teach identifying a transcribed region that is an operon.

However, Leary et al. teach mapping transcripts with the same 5' end to a viral genome. Leary et al. state that their method, referred to as "FAT", is particularly useful for identifying genes whose transcripts have common ends, and that genes are temporally regulated such as herpes simplex virus type I. See page 3.

Darnell et al. teach that operon are part of a genome from which a single transcript comprises multiple genes and the production of this transcript, i.e. transcription, is temporally regulated, e.g. the lactose operon regulated by the presence of lactose. See pages 284 and 285.

Given that the transcripts for each of the genes comprised in an operon can be interpreted as having common ends, and that Leary et al. motivate using their method for genes that are temporally regulated and for transcripts that have a common end, one having ordinary skill in the art at the time the invention was made would therefore have been motivated to modify Leary et al. to modify the methods of Leary et al. and Lockhart et al. to apply the methods for mapping transcripts to all genes whose transcription are temporally regulated and whose transcripts have common ends, such as those of an operon.

***Claim Objection***

12. Claim 3 is objected to because of the following informalities: Claim 3 is written as a claim depending from itself. Appropriate correction is required.

***Conclusion***

13. No claim is allowed.

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shubo (Joe) Zhou, whose telephone number is 571-272-0724. The examiner can normally be reached Monday-Friday from 8 A.M. to 4 P.M. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel, Ph.D., can be reached on 571-272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to Patent Analyst Tina Plunkett whose phone number is (571) 272-0549.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete

service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public. For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

Shubo (Joe) Zhou, Ph.D.

Patent Examiner

ARDIN H. MARSCHEL
PRIMARY EXAMINER

5/31/05